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Chapter 52: Headache: Migraine and Tension-Type

MIGRAINE HEADACHE

- *Migraine* is a common, recurrent headache of moderate-to-severe intensity that disrupts normal functioning and is linked with gastrointestinal (GI), neurologic, and autonomic symptoms. In migraine with aura, focal neurologic symptoms occur before or during the headache.

CLINICAL PRESENTATION

- Migraine headache is characterized by recurring episodes of throbbing head pain, frequently unilateral.
- About 77% of patients with migraines experience premonitory symptoms in the hours or days before a headache, distinct from aura. Common symptoms include neurologic issues like phonophobia, photophobia, hyperosmia, and difficulty concentrating, along with psychological, autonomic, and constitutional symptoms such as anxiety, depression, irritability, polyuria, diarrhea, stiff neck, yawning, and food cravings.
- About one-third of patients with migraine experience an aura, which develops over 5–20 minutes and lasts under 60 minutes. Visual auras may include positive features like flashes or shimmering lights and negative features like blind spots. Sensory symptoms such as paresthesias, numbness in the arms and face, dysphasia, aphasia, weakness, and hemiparesis can also occur.
- Migraine headache pain usually starts gradually, peaks within minutes to hours, and lasts 4–72 hours. It is typically moderate to severe, unilateral, and throbbing, often in the frontotemporal region. GI symptoms like nausea and vomiting commonly accompany the headache. Other symptoms include anorexia, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, sweating, facial pallor, and localized facial or scalp swelling. Sensory hyperacuity (photophobia, phonophobia, or osmophobia) is common, and many patients seek a dark, quiet place.
- Once the headache pain wanes, a resolution phase characterized by exhaustion, malaise, and irritability ensues.

DIAGNOSIS

- Diagnosis is based on monthly migraine days (MMDs) and monthly headache days (MHDs). Episodic migraine is diagnosed with fewer than 15 MMDs or MHDs per month, while chronic migraine requires at least 15 MHDs per month for 3 months, with at least 8 being MMDs.
- A comprehensive headache history should cover age at onset, attack frequency, timing, duration, triggers, alleviating factors, symptom characteristics, associated symptoms, treatment history, and family and social history.
- Neuroimaging should be considered in patients with unexplained abnormal neurologic examination or atypical headache history.
- Migraine onset after age 50 suggests an organic cause, like a mass lesion, cerebrovascular disease, or temporal arteritis.

TREATMENT

- Goals of Treatment: The goals are to prevent headaches, provide quick relief with minimal adverse effects, minimize disability and distress, enable normal activities, and manage headaches without emergency or doctor visits.

NONPHARMACOLOGIC TREATMENT

- Apply ice to the head and recommend resting or sleeping in a dark, quiet environment.

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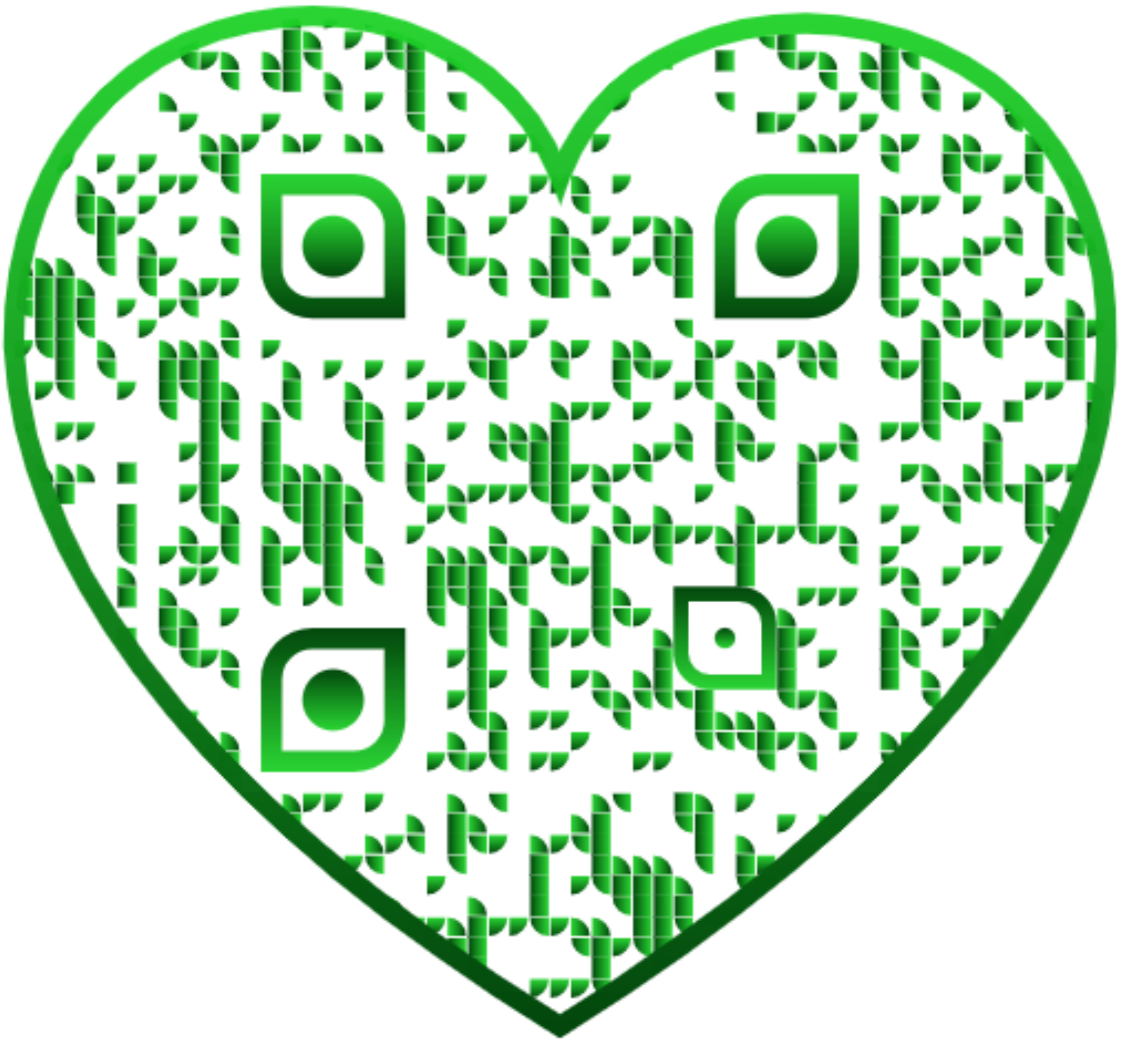

- Identify and avoid triggers of migraine attacks (**Table 52-1**).
- Behavioral interventions like relaxation, biofeedback, and cognitive therapy can help alone or when medications don't work or are not tolerated.
- The neuromodulation devices approved by the Food and Drug Administration (FDA) can be used alongside other treatments for migraine prevention and management.

TABLE 52-1

Commonly Reported Triggers of Migraine

Food Triggers	
Alcohol	Monosodium glutamate (eg, in Chinese food, seasoned salt, and instant foods)
Excessive caffeine/caffeine withdrawal	Nitrate-containing foods (eg, processed meats)
Chocolate	Saccharin/aspartame (eg, diet foods or diet sodas)
Fermented and pickled foods	Tyramine-containing foods
Environmental Triggers	
Glare or flickering lights High altitude Loud noises	Strong smells and fumes Tobacco smoke Weather changes
Behavioral–Physiologic Triggers	
Excess or insufficient sleep Fatigue Menstruation, menopause Sexual activity	Skipped meals/fasting Strenuous physical activity (eg, prolonged overexertion) Stress or poststress

PHARMACOLOGIC TREATMENT

- Administer acute migraine therapies at the onset of migraine (**Table 52-2** and **Fig. 52-1**).

FIGURE 52-1

Treatment algorithm for acute migraine headaches.

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TABLE 52-2

Pharmacokinetic Characteristics of Triptans

Medication	Half-Life (Hours)	Time to Maximal Concentration (t_{max})	Bioavailability (%)	Elimination
Almotriptan	3–4	1.4–3.8 hours	80	MAO-A, CYP3A4, CYP2D6
Eletriptan	4–5	1–2 hours	50	CYP3A4
Frovatriptan	25	2–4 hours	24–30	Mostly unchanged, CYP1A2
Naratriptan	5–6	2–3 hours	63–74	Largely unchanged, CYP450 (various isoenzymes); primary sulfa medication
Rizatriptan	2–3		45	MAO-A
Oral tablets		1–1.2 hours		
Disintegrating		1.6–2.5 hours		
Sumatriptan	2			MAO-A; primary sulfa medication
Subcutaneous injection		12–15 minutes	97	
Oral tablets		2.5 hours	14	
Nasal spray		10 minutes	17	
Nasal powder		45 minutes		
Zolmitriptan	3		40–48	CYP1A2, MAO-A
Oral		2 hours		
Disintegrating		3.3 hours		
Nasal		4 hours		

CYP, cytochrome P450; MAO-A, monoamine oxidase type A.

Antiemetic Pretreatment

- When nausea and vomiting are severe, pretreat with an oral or rectal antiemetic, like **metoclopramide**, **chlorpromazine,** or **prochlorperazine,** 15–30 minutes before migraine treatment. Metoclopramide also reverses gastroparesis and improves oral medication absorption.
- Prochlorperazine (intramuscular [IM], intravenous [IV], rectal), metoclopramide (IV), and parenteral chlorpromazine and **droperidol** offer more effective pain relief than a placebo.

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Analgesics and Nonsteroidal Anti-inflammatory Drugs

- Simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatments for mild-to-moderate migraines and can help with some severe attacks. Effective options include **aspirin, diclofenac**, **ibuprofen, naproxen sodium, celecoxib,** and **acetaminophen** combined with **aspirin** and **caffeine.**
- NSAIDs may prevent inflammation in the trigeminovascular system by inhibiting prostaglandin synthesis.
- Rectal analgesics are an option for patients with severe nausea and vomiting.
- Prescription combinations of aspirin or acetaminophen with **butalbital** are available. However, use should be limited due to risks of overuse, medication-overuse headache, and withdrawal.
- Metoclopramide with aspirin is as effective as sumatriptan and can be used when triptans are contraindicated.

Ergot Alkaloids and Derivatives

- Ergot alkaloids are effective for moderate-to-severe migraines. They are nonselective 5-HT_1 receptor agonists that constrict intracranial blood vessels and inhibit neurogenic inflammation, causing venous and arterial constriction.
- **Ergotamine tartrate** is available for oral, sublingual, and rectal use. Oral and rectal forms include caffeine to improve absorption and enhance analgesia.
- **Dihydroergotamine (DHE)** can be self-administered IM or subcutaneous (SC), with IV administration done in the hospital. The nasal spray form is also effective.
- Ergotamine derivatives often cause nausea and vomiting, so consider antiemetic pretreatment and adjust the dose to avoid nausea. Other adverse effects include abdominal pain, weakness, fatigue, paresthesia, muscle pain, diarrhea, and chest tightness. Severe peripheral ischemia (ergotism) symptoms include cold, numb, painful extremities; continuous paresthesias; diminished pulses; and claudication. Rarely, ergotamine can cause gangrene, myocardial infarction, hepatic necrosis, and ischemia in the bowel and brain. Avoid using ergotamine derivatives and triptans within 24 hours of each other.
- Ergot derivatives are contraindicated in renal and hepatic failure, vascular diseases, uncontrolled hypertension, sepsis, and in pregnant or nursing individuals.
- DHE does not seem to cause rebound headaches, but ergotamine tartrate dosage should be strictly limited to prevent them.

Serotonin Receptor Agonists (Triptans)

- Triptans are suitable first-line treatments for mild-to-severe migraines or as a backup when nonspecific medications fail.
- As selective 5-HT_{1B} and 5-HT_{1D} receptor agonists, triptans relieve migraines by normalizing dilated intracranial arteries, inhibiting the release of vasoactive peptide, and blocking transmission through second-order neurons to the thalamus.
- **Sumatriptan** SC is available as an autoinjector for self-administration, providing enhanced efficacy and faster onset. Intranasal sumatriptan also acts quickly and is similarly effective to the oral form.
- Triptans are categorized by onset and efficacy: sumatriptan, **rizatriptan**, **zolmitriptan, almotriptan**, and **eletriptan** have a faster onset and higher efficacy. **Naratriptan** and **frovatriptan** have a slower onset, lower efficacy, longer half-lives, and less headache recurrence, suitable for slower onset, longer duration migraines. Pharmacokinetic characteristics of the triptans are shown in **Table 52-3**.
- If one triptan is ineffective, another may still work.
- Triptan adverse effects include paresthesias, fatigue, dizziness, flushing, warmth, and drowsiness. SC use may cause minor injection site reactions, while intranasal use can lead to taste changes and nasal discomfort.

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- Up to 25% of patients report chest tightness, pressure, heaviness, or pain in the chest, neck, or throat. Though rare, a myocardial infarction or coronary vasospasm has been reported. Use triptans cautiously in those at risk for coronary artery disease and assess cardiovascular risk before giving them to menopausal individuals, men over 40, and patients with uncontrolled risk factors. The first dose should be given under medical supervision. Contraindications include ischemic heart disease, uncontrolled hypertension, cerebrovascular disease, hemiplegic and basilar migraine, and pregnancy.
- Avoid administering triptans within 24 hours of ergotamines or within 2 weeks of MAO inhibitors. Triptans with serotonin antidepressants may cause serotonin syndrome. Do not use eletriptan with CYP3A4 inhibitors like macrolide antibiotics, antifungals, and some antivirals.

TABLE 52-3

Dosing of Self-administered Acute Migraine Therapies

Medication	Dose	Maximum Dose/Comments
Nonspecific Therapies		
Analgesics		
Acetaminophen[a] (Tylenol)	500–1000 mg every 4–6 hours as needed	Maximum daily dose is 4 g
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
Aspirin[a]	500–1000 mg every 4–6 hours as needed	Maximum daily dose is 4 g
Ibuprofen[a] (Advil, Motrin)	400–800 mg every 4–6 hours as needed	Maximum daily dose is 3.2 g
Naproxen sodium[a] (Aleve, Anaprox)	220–550 mg every 8–12 hours as needed	Avoid doses greater than 1.375 g/day
Diclofenac potassium[a] (Cataflam)	50–100 mg every 8 hours as needed	Avoid doses greater than 150 mg/day
Diclofenac potassium powder[a] (Cambia)	50 mg orally mixed in 1–2 ounces (30–60 mL) of water	Use the lowest effective dose for the shortest duration
Ketorolac nasal (Sprix)	31.5 mg (one spray each nostril) every 6–8 hours as needed	Maximum daily dose is 126 mg/day × 5 days
Ketorolac IM[b]	30–60 mg every 6 hours as needed	Maximum daily dose is 120 mg/day × 5 days
Celecoxib solution (25 mg/1 mL)[a] (Elyxyb)	120 mg as needed	Maximum daily dose is 120 mg/day; use for the fewest days per month as necessary
Combination Products		
Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg[a] (Excedrin Migraine)	Two tablets every 6 hours as needed	Available over-the-counter as Excedrin Migraine
Acetaminophen 325 mg, isometheptene 65 mg, and	Two capsules followed by one capsule every hour until relief is obtained	Midrin has been removed from the market, but guidelines still mention it.;

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dichloralphenazone 100 mg (Midrin)		Maximum five capsules/12 hours
Sumatriptan and naproxen (Treximet) 85/500 and 10/60	1 tablet at migraine onset, may repeat in 2 hours	
Ergotamine 1 mg and caffeine 100 mg tablet[b] (Cafergot)	2 mg at onset; can repeat 1–2 mg every 30 minutes as needed	Maximum dose is 6 mg/day or 10 mg/week; consider antiemetic pretreatment
Ergotamine 2 mg and caffeine 100 mg rectal suppository[b] (Cafergot, Migergot)	Insert half to one suppository at onset; can repeat after 1 hour if needed	Maximum dose is 4 mg/day or 10 mg/week; consider antiemetic pretreatment
Butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg (Fioricet)	2 tablets at onset, then 1 tablet every 6 hours PRN	Not recommended, use as a last resort
Butalbital 50 mg, aspirin 325 mg, and caffeine 40 mg (Fiorinal)	2 tablets at onset, then 1 tablet every 6 hours PRN	Not recommended, use as a last resort
Anti-dopaminergic Medications		
Metoclopramide[b] (Reglan)	10 mg every 4–6 hours as needed	Maximum daily dose is 40 mg (also available as ODT)
Prochlorperazine[b] (Compazine)	5–10 mg orally 3–4 times daily as needed or 25 mg via rectal suppository up to twice daily as needed	Maximum daily dose is 40 mg for oral and 50 mg for suppository
Promethazine (Phenergan)	25 mg oral or via rectal suppository every 4–6 hours as needed	Maximum daily dose is 100 mg
Migraine-Specific Therapies		
Ergotamine Tartrate		
Sublingual tablet (2 mg) (Ergomar)	2 mg at onset; can repeat 2 mg every 30 minutes as needed	Maximum dose is 4 mg/day or 10 mg/wk; consider antiemetic pretreatment
Dihydroergotamine		
Injection 1 mg/mL (D.H.E. 45)[b]	0.25–1 mg (IM, IV, or SC) at onset; can repeat every hour as needed	Maximum dose is 3 mg/day or 6 mg/wk
Nasal spray 4 mg/mL[a] (Migranal, Trudhesa)	Migranal: One spray (0.5 mg) in each nostril at onset; can repeat 15 minutes later (total dose is 2 mg or four sprays) Trudhesa: 0.725 mg (one spray) in each nostril, may repeat once in 1 hour	Migranal: Maximum dose is 3 mg/day or 6 mg/wk; prime sprayer four times before using; do not tilt head back or inhale through nose while spraying; discard open ampules after 8 hours Trudhesa: Two (four sprays)/day or three (six sprays)/week
Triptans		

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Sumatriptan[a]		
Injection (Imitrex, Zembrace Symtouch)	3–6 mg subcutaneous at onset; can repeat after 1 hour if needed	Maximum daily dose is 12 mg
Oral tablets (Imitrex)	25, 50, or 100 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 200 mg; combination product with naproxen, 85/500 mg
Nasal spray (Imitrex)	5 or 20 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 40 mg
Nasal spray (Tosymra)	10 mg intranasally at onset; can repeat after 1 hour if needed	Maximum daily dose is 30 mg
Nasal powder (Onzetra Xsail)	22 mg (one 11-mg nosepiece in each nostril) at onset; can repeat after 2 hours if needed	Maximum daily dose is 44 mg (four nosepieces, 11 mg each)
Zolmitriptan[a]		
Oral tablets/ODT (Zomig, Zomig-ZMT)	2.5 or 5 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg; do not divide ODT dosage form
Nasal spray (Zomig)	2.5 or 5 mg intranasally at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg
Naratriptan[a] (Amerge)	1 or 2.5 mg at onset; can repeat after 4 hours if needed	Maximum daily dose is 5 mg
Rizatriptan[a] oral tablets/ODT (Maxalt, Maxalt-MLT)	5 or 10 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 30 mg; use 5 mg dose (15 mg/day maximum) in individuals on propranolol
Almotriptan[a] (Axert)	6.25 or 12.5 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 25 mg
Frovatriptan[a] (Frova)	2.5 or 5 mg at onset; can repeat in 2 hours if needed	Maximum daily dose is 7.5 mg
Eletriptan[a] (Relpax)	20 or 40 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 80 mg
Ditans		
Lasmiditan[a] (Reyvow)	50, 100, or 200 mg at onset	Maximum of one dose per 24 hours; safety of treating more than four migraine attacks in a 30-day period has not been established
CGRP Antagonists		
Ubrogepant[a] (Ubrelvy)	50 or 100 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 200 mg; safety of treating more than eight migraine attacks in a 30-day period has not been established
Rimegepant[a] (Nurtec ODT)	75 mg at onset	Maximum of one dose per 24 hours; take on an empty stomach and 16 days per month (every other day when using for prophylaxis)

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Zavegepant nasal spray[a] (Zavzpret)	10 mg intranasally at onset	Maximum daily dose is 10 mg; safety of treating more than 8 migraine attacks in a 30-day period has not been established

ODT, orally disintegrating tablet.

[a]Level A—established efficacy (more than two Class I studies).

[b]Level B—probably effective (one Class I or two Class II studies).

Ditans

- **Lasmiditan** belongs to a new class of migraine medications called "ditans," which block neurogenic inflammation in the dura and stimulate the trigeminal nucleus caudalis.

  ✓ Common adverse effects include dizziness, paresthesia, sedation, and nausea/vomiting. It includes a warning to avoid driving or operating heavy machinery for at least 8 hours after each dose due to drowsiness. Ditans are not contraindicated in cardiovascular disease.

Calcitonin Gene-Related Peptide (CGRP) Antagonists

- **Ubrogepant, rimegepant**, and **zavegepant** known as "gepants," block CGRP receptors to cause vasoconstriction and reduce neurogenic inflammation.
- They have similar efficacy to triptans and lasmiditan but are often better tolerated. They are not contraindicated for those with cardiovascular disease, and do not cause medication overuse headaches.

  ✓ Adverse medication effects include nausea, xerostomia, nasal irritation, altered taste, and somnolence.

  ✓ Rimegepant has an 11-hour half-life and shouldn't be redosed within 24 hours. Ubrogepant has a 5–7-hour half-life and can be redosed 2 hours after the first dose. Zavegepant has a 7-hour half-life and should not be redosed within 24 hours.

  ✓ Avoid using gepants with strong CYP3A4, P-glycoprotein, and breast cancer resistance protein inhibitors. Zavegepant should not be redosed within 24 hours. Gepants should be avoided in severe renal or hepatic impairment.

Opioids

- Opioid analgesics like **butorphanol**, **meperidine**, **methadone**, **tramadol**, and **codeine** lack strong evidence for treating acute migraine. Oral codeine or tramadol with acetaminophen is likely effective, and butorphanol nasal spray is proven effective.
- Reserve opioids for patients with infrequent, moderate-to-severe headaches when conventional therapies are contraindicated or ineffective. Therapy should be closely supervised.

Additional Treatment Considerations

- Outpatient rescue medications include subcutaneous sumatriptan, IM ketorolac, or corticosteroids like dexamethasone. In emergency or inpatient settings, IV options like DHE, antiemetics, valproate sodium, corticosteroids, and magnesium sulfate are common.
- Frequent use of acute migraine medications can lead to medication-overuse headaches, often with analgesics, opioids, ergotamine, and triptans. Limit therapy use to 15 days or less per month.

Preventative Pharmacologic Therapy

- Preventative therapies (**Table 52-4** and **Fig. 52-2**) are taken daily to reduce attack frequency, severity, and duration, and to improve response to

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acute treatments.

- Consider preventative therapy for recurring migraines causing significant disability, frequent attacks needing medication over twice a week, ineffective or harmful symptomatic therapies, severe disruption or neurologic risk, or patient preference to reduce attacks. It can be used intermittently for predictable migraine patterns, like exercise-induced or menstrual migraines.
- Choose preventive therapy based on evidence of efficacy, adverse effects, and individual comorbidities. Response is unpredictable, and it may take up to 6 months to see benefits.
- Only **propranolol**, **timolol**, divalproex sodium, **topiramate,** CGRP inhibitors, and **onabotulinumtoxinA** are FDA-approved for migraine prevention. Other agents may also have probable efficacy.
- Start at low doses and increase slowly until effective or intolerable. Continue for 6–12 months after improvement, then consider tapering or stopping.

FIGURE 52-2

Treatment algorithm for preventive management of migraine headaches. (NSAID, nonsteroidal anti-inflammatory drug.)

TABLE 52-4

Dosing of Preventive Migraine Therapies

Medication	Initial Dose	Usual Range	Comments
β-Adrenergic Antagonists			
Atenolol[a] (Tenormin)	25–50 mg/day	50–200 mg/day	
Metoprolol[b] (Toprol, Toprol XL)	25–100 mg/day in divided doses	100–200 mg/day in divided doses	Dose short-acting two to four times a day and extended-release one to two times a day
Nadolol[a] (Corgard)	40–80 mg/day	80–240 mg/day	
Propranolol[b] (Inderal, Inderal LA)	40 mg/day in divided doses	40–160 mg/day in divided doses	Dose short-acting two to three times a day and extended-release one to two times a day
Timolol[b] (Blocadren)	20 mg/day in divided doses	20–60 mg/day in divided doses	
Antidepressants			
Amitriptyline[a] (Elavil)	10 mg at bedtime	20–50 mg at bedtime	
Duloxetine (Cymbalta)	20–30 mg/day	Up to 60 mg/day	
Nortriptyline (Pamelor)	10 mg at bedtime	Up to 100 mg at bedtime	
Venlafaxine[a] (Effexor, Effexor-XR)	37.5 mg/day	75–150 mg/day	Dose short-acting twice a day and extended-release once daily

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Antiseizure Medications			
Topiramate[b] (Topamax)	12.5–25 mg/day	50–200 mg/day in divided doses or only at bedtime	Increase by 12.5–25 mg/wk
Valproic acid/divalproex sodium[b] (Depakene, Depakote, Depakote ER)	250–500 mg/day in divided doses, or daily for extended-release	500–1,500 mg/day	Dose short-acting twice a day and extended-release once daily; monitor levels if adherence is an issue
Miscellaneous			
OnabotulinumtoxinA[b] (Botox)	155 units IM every 12 weeks	155–195 units	Approved for chronic migraine treatment only
CGRP Antagonists (Anti-CGRP Antibodies)			
Erenumab-aooe[b] (Aimovig)	70 mg subcutaneously every month	70–140 mg subcutaneously every month	
Fremanezumab-vfrm[b] (Ajovy)	225 mg subcutaneously every month or 675 mg subcutaneously every 3 months	225 mg subcutaneously every month or 675 mg subcutaneously every 3 months	
Galcanezumab-gnlm[b] (Emgality)	240 mg subcutaneous loading dose, followed by 120 mg subcutaneously every month	120 mg subcutaneously every month	
Eptinezumab-jjmr[b] (Vyepti)	100 mg via IV infusion over 30 minutes every 3 months	100–300 mg IV infusion over 30 minutes every 3 months	
CGRP Antagonists ("Gepants")			
Atogepant[b] (Quilpta)	10 mg/day	60 mg/day	Taken with or without food
Rimegepant[b] (Nurtec ODT)	75 mg every other day	75 mg/day	No titration required and taken on an empty stomach
Antihypertensive Medications			
Lisinopril (Zestril)[a]	5–10 mg/day	10–25 mg/day	
Candesartan (Atacand)[b]	8 mg/day	8–32 mg/day	
NMDA Antagonists			
Memantine (Namenda)[a]	5–10 mg/day	10–20 mg/day	
Nonsteroidal Anti-inflammatory Drugs—For Prevention of Menstrual Migraine Only			
Ibuprofen (Motrin)	200 mg/day in three to four divided doses	200–800 mg/day in three to four divided doses (maximum daily	Use intermittently only; daily or prolonged use may lead to medication-

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		dose is 3200 mg)	overuse headaches
Ketoprofen (Orudis)	150 mg/day in divided doses	150 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Naproxen sodium (Aleve, Anaprox)	550 mg/day in divided doses	550–1100 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Triptans—For Prevention of Menstrual Migraine Only			
Frovatriptan[b] (Frova)	2.5 mg/day or 5 mg/day in divided doses; start 6 days before the anticipated start of menstruation	5 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Naratriptan (Amerge)	2 mg/day in divided doses; start 6 days before the anticipated start of menstruation	2 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Zolmitriptan (Zomig)	5–7.5 mg/day in divided doses; start 6 days before the anticipated start of menstruation	5–7.5 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Miscellaneous			
Magnesium	400 mg/day	800 mg/day in divided doses	May be more helpful in migraine with aura and menstrual migraine
MIG-99[a] (feverfew)	10–100 mg/day in divided doses	Same as initial dose	Withdrawal may be associated with increased headaches
Petasites	100–150 mg/day in divided doses	150 mg/day in divided doses	Use only in commercial preparations; plant is carcinogenic
Riboflavin	400 mg/day in divided doses	400 mg/day in divided doses	Benefit only after 3 months

ODT, orally disintegrating tablet.

[a]Level B—probably effective (one Class I or two Class II trials based on American Academy of Neurology evidence classification).

[b]Level A—established efficacy (two or more Class I trials based on American Academy of Neurology evidence classification).

β-Adrenergic antagonists

- Propranolol, timolol, and **metoprolol** halve migraine frequency in over 50% of patients. **Atenolol** and **nadolol** are likely effective as well.

  ✓ Adverse effects include drowsiness, fatigue, sleep issues, vivid dreams, memory problems, depression, sexual dysfunction, bradycardia, and hypotension.

  ✓ Use cautiously in patients with heart failure, peripheral vascular disease, atrioventricular conduction issues, asthma, depression, and

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diabetes.

Antidepressants

- **Amitriptyline** and **venlafaxine**, both tricyclic antidepressants (TCAs), are likely effective for migraine prevention. Data is insufficient for other antidepressants.
- Their migraine prevention benefits are not tied to antidepressant effects and may involve downregulating central 5-HT_2 receptors, increasing synaptic norepinephrine, and enhancing opioid receptor actions.

  ✓ TCAs are generally well tolerated for migraine prevention; however, anticholinergic effects may limit their use, especially in older patients or those with benign prostatic hyperplasia or glaucoma. Evening doses help with sedation. They may cause increased appetite, weight gain, orthostatic hypotension, and occasionally, slowed atrioventricular conduction.

Antiseizure medications

- **Valproic acid**, **divalproex sodium,** and **topiramate** can decrease headache frequency, severity, and duration. **Carbamazepine, gabapentin,** and **pregabalin** are possibly effective, while **lamotrigine** is likely ineffective.

  ✓ Valproic acid and divalproex sodium can cause nausea, tremor, drowsiness, weight gain, hair loss, and hepatotoxicity. Conduct baseline liver tests. The extended-release form of divalproex sodium is taken once daily and is better tolerated than the enteric-coated version. Valproate is contraindicated in pregnancy and in patients with pancreatitis or chronic liver disease.

  ✓ Common adverse effects of topiramate include paresthesias (~50% of patients) and weight loss (9%–12%). Other effects are fatigue, anorexia, diarrhea, memory issues, language problems, taste changes, and nausea. Use cautiously in patients with a history of kidney stones or cognitive impairment.

Nonsteroidal anti-inflammatory drugs

- For predictable migraine patterns like menstrual migraines, intermittent use may help. Start up to 1 week before vulnerability and continue until it passes. Naproxen has the strongest evidence for efficacy, while aspirin has the weakest.

  ✓ Potential GI and renal toxicity limit daily or prolonged use.

Triptans

- Frovatriptan is proven effective for prevention, while naratriptan and zolmitriptan are likely effective. Begin treatment 1–2 days before the expected headache onset and continue during vulnerability.

Calcitonin gene-related peptide antagonists (anti-CGRP antibodies)

- Monoclonal antibodies targeting the CGRP receptor (**erenumab-aooe, fremanezumab-vfrm, eptinezumab-jjmr**, and **galcanezumab-gnlm**) are effective for preventing episodic and chronic migraines. However, their use may be limited by cost and access.

  ✓ Injection site reactions are the most common adverse effect for subcutaneous agents. Others include constipation, nasopharyngitis, and hypersensitivity. There are no known drug interactions. However, avoid this within 6 months of a cardiovascular event.

Miscellaneous prophylactic agents

- The angiotensin-converting enzyme inhibitor **lisinopril** and the angiotensin II receptor blocker **candesartan** are effective for migraines. The calcium channel blocker **verapamil** is also widely used. **Clonidine** and **guanfacine** show possible efficacy, but adverse effects limit use.
- **Cyproheptadine** has also been shown to be effective.

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- Localized injections of **botulinum toxin type A** is FDA-approved and is considered second-line treatment.
- Nutraceuticals like **coenzyme Q10, magnesium,** and **riboflavin** are used for migraine prevention.
- Monitor patients taking abortive therapy for frequency of use of prescription and nonprescription medications and for adverse effects.
- Track abortive medication use to determine the need for preventative therapy. Monitor preventative therapy for adverse effects, abortive needs, proper dosing, and compliance.

TENSION-TYPE HEADACHE

- *Tension-type headache*, the most common primary headache, occurs more often in females. Pain is typically mild to moderate and nonpulsatile. These headaches are classified as episodic (infrequent or frequent) or chronic based on attack frequency and duration.

CLINICAL PRESENTATION

- Premonitory symptoms and aura are absent. Pain is typically mild to moderate, bilateral (hatband pattern), and nonpulsatile.
- Mild photophobia or phonophobia may occur, and some patients may have tender spots or nodules in pericranial or cervical muscles.
- A comprehensive headache history should cover onset age, frequency, timing, duration, triggers, relieving factors, symptom characteristics, associated symptoms, treatment history, and family and social history.
- Headaches are classified as infrequent episodic, frequent episodic, or chronic.

TREATMENT

- Goals of Treatment: Pain relief and preventing further headaches.

NONPHARMACOLOGIC THERAPY

- Nonpharmacologic therapies include reassurance, counseling, stress management, relaxation training, and biofeedback. Evidence for physical therapies like heat/cold packs, ultrasound, nerve stimulation, massage, acupuncture, trigger point injections, and occipital nerve blocks is inconsistent. Identification of triggers and lifestyle modification can help.

PHARMACOLOGIC THERAPY

Acute Treatment

- Simple analgesics (alone or with caffeine) and NSAIDs are primary acute treatments. Effective options include **acetaminophen, aspirin, diclofenac, ibuprofen, naproxen, ketoprofen,** and **ketorolac.**
- **Aspirin** or **acetaminophen** combined with butalbital is effective. Codeine may work for some, but combinations with butalbital and codeine should be avoided due to overuse risks. Muscle relaxants lack evidence of efficacy.
- **Limit acute medication for episodic headaches, especially butalbital or combination analgesics, to 10 days per month.**

Preventative Therapy

- Use preventive treatment if headaches occur over twice a week, last longer than 3–4 hours, or cause significant disability.
- TCAs are commonly used for tension headache prevention. **Venlafaxine**, **mirtazapine, gabapentin, topiramate, valproate**, and **tizanidine** may also be effective. Limited data suggest **lidocaine** trigger point injections might reduce headache frequency, while **botulinum toxin** results are inconsistent.

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EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor headache frequency, intensity, duration, and changes in pattern. Encourage patients to use a headache diary to track these aspects and identify triggers.

See Chapter 84, Primary Headache Disorders, authored by Natalie T. Heinrich, Michelle Maynard, and Millad J. Sobhanian for a more detailed discussion of this topic.

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